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> d his

(FILE 'HOME' ENTERED AT 15:23:49 ON 04 DEC 2003)

FILE 'MEDLINE' ENTERED AT 15:23:56 ON 04 DEC 2003

```
L1         17936 S DRUG? (P) INTERACTION
L2          2378 S DRUG? INTERACTION
L3           256 S L2 AND REVIEW?
L4            20 S L2 AND (HMG COA REDUCTASE)
L5           256 S L3 AND REVIEW?
L6             1 S L4 AND REVIEW?
L7             0 S L1 AND (HMG CA REDUCTASE) AND REVIEW?
L8          3803 S HMG COA REDUCTASE
L9            58 S L1 AND L8
L10            5 S L9 AND REVIEW?
L11            4 S L10 NOT L6
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=>

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=> d bib abs

L6 ANSWER 1 OF 1 MEDLINE on STN
AN 2003495827 IN-PROCESS
DN 22934468 PubMed ID: 14574085
TI The Safety of **HMG-CoA Reductase** Inhibitors in Special Populations at High Cardiovascular Risk.
AU Corsini Alberto
CS Department of Pharmacological Sciences, University of Milan, via Balzaretti 9, 20133 Milan, Italy.. alberto.corsini@unimi.it
SO CARDIOVASCULAR DRUGS AND THERAPY, (2003 May) 17 (3) 265-85. Journal code: 8712220. ISSN: 0920-3206.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20031024
Last Updated on STN: 20031024
AB Controlled clinical studies and clinical experience over many years have proven that virtually all patients benefit from lipid-lowering therapy with statins, even those with normal LDL cholesterol levels. Several recent large outcome trials have further demonstrated the clinical benefits and safety of statins in patients with a wide-range of high risks for cardiovascular disease. Those patients at highest absolute cardiovascular risk generally have the most to gain from statin therapy. A variety of statins are available to lower plasma lipids to guideline levels, but all differ in their pharmacokinetic properties, **drug interaction** profiles, and risk of myotoxicity. This has been highlighted by the withdrawal of cerivastatin from the market as a result of serious safety concerns. This **review** examines the safety and effectiveness of statins in special populations at high risk of cardiovascular disease-patients with coronary heart disease, dyslipidaemia, diabetes, hypertension, nephrotic disease, HIV, organ transplant patients and the elderly-with a focus on clinically relevant differences in the properties of individual statins that may influence the risk of drug interactions and side effects.

=> s l1 and (hmg ca reductase) and review?
7768 HMG
106336 CA
50066 REDUCTASE
0 HMG CA REDUCTASE
(HMG(W)CA(W)REDUCTASE)
511999 REVIEW?
L7 0 L1 AND (HMG CA REDUCTASE) AND REVIEW?

=> s hmg coa reductase
7768 HMG
25419 COA
50066 REDUCTASE
L8 3803 HMG COA REDUCTASE
(HMG(W)COA(W)REDUCTASE)

=> s l1 and l8
L9 58 L1 AND L8

=> s l9 and review/
'REVIEW/' IS NOT A VALID FIELD CODE
For a list of field codes for the current file, enter "HELP SFIELDS" at an arrow prompt (=>).

=> s l9 and review?
511999 REVIEW?
L10 5 L9 AND REVIEW?

=> s l10 not l6
L11 4 L10 NOT L6

=> d 1-4 bib abs

L11 ANSWER 1 OF 4 MEDLINE on STN
AN 2003180148 MEDLINE
DN 22584818 PubMed ID: 12699076
TI Lymphocyte function-associated antigen-1 blockade by statins: molecular basis and biological relevance.
AU Weitz-Schmidt Gabriele
CS Novartis Pharma AG, Preclinical Research, Basel, Switzerland..

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gabriele.weitz@pharma.novartis.com
SO ENDOTHELIUM, (2003) 10 (1) 43-7. Ref: 41
Journal code: 9412590. ISSN: 1062-3329.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030418
Last Updated on STN: 20030802
Entered Medline: 20030801
AB Lymphocyte function-associated antigen-1 (LFA-1) belongs to the integrin family and plays an important role in leukocyte trafficking and in T-cell activation. Random screening of chemical libraries identified the 3-hydroxy-3-methylglutaryl coenzyme A (**HMG-CoA**) **reductase** inhibitor lovastatin as an inhibitor of the LFA-1/intercellular adhesion molecule (ICAM)-1 **interaction**. The effect of lovastatin on LFA-1 was found to be unrelated to the inhibition of **HMG-CoA reductase** and to be mediated by lovastatin binding to a novel allosteric site within LFA-1. The biological relevance of LFA-1 inhibition by statins with respect to the overall benefit of this **drug** class is **reviewed**. The implications of the statin effect on LFA-1 for future **drug** design and therapy are discussed.

L11 ANSWER 2 OF 4 MEDLINE on STN
AN 2001535976 MEDLINE
DN 21466754 PubMed ID: 11583063
TI The role of cytochrome P450-mediated drug-drug interactions in determining the safety of statins.
AU Worz C R; Bottorff M
CS Department of Pharmacy, University of Cincinnati, Ohio, USA.. crw@skilledcare.com
SO Expert Opin Pharmacother, (2001 Jul) 2 (7) 1119-27. Ref: 47
Journal code: 100897346. ISSN: 1465-6566.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20011004
Last Updated on STN: 20011029
Entered Medline: 20011025
AB The objectives of this **review** are to discuss the role of cytochrome P450 (CYP450) isoforms in **drug** metabolism, to explain differences in metabolism among the **HMG-CoA reductase** inhibitors (HMGs, statins), to **review** **drug-drug** and **drug-food interaction** studies dealing with the HMGs, to present case reports dealing with HMG-related myopathy, to discuss major clinical implications of these case reports and to express an opinion of use of HMGs in clinical practice.

L11 ANSWER 3 OF 4 MEDLINE on STN
AN 1999431277 MEDLINE
DN 99431277 PubMed ID: 10503952
TI Clinical pharmacology of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.
AU Moghadasian M H
CS Department of Pathology and Laboratory Medicine, St. Paul's Hospital and University of British Columbia, Vancouver, Canada.. mhmoghad@unixg.ubc.ca
SO LIFE SCIENCES, (1999) 65 (13) 1329-37. Ref: 59
Journal code: 0375521. ISSN: 0024-3205.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007
AB In this article, de novo cholesterol synthesis, its inhibition by **HMG-CoA reductase** inhibitors (statins) and

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clinical pharmacology aspects of the statins have been **reviewed**. Statins are available in both active and pro-**drug** forms. Their affinity to bind and subsequently to inhibit **HMG-CoA reductase** activity is approximately 3 orders of magnitude higher than that of natural substrate (HMG-CoA). All members of this group of lipid-lowering agents are, to a varying degree, absorbed from the gut. However, their bioavailability depends on their lipophobicity and their concomitant use with meals. The **interaction** between **HMG -CoA reductase** inhibitors and other lipid-lowering agents has been **reviewed** in more detail. One major side-effect of lipid-lowering combination therapy is myopathy with or without rhabdomyolysis. Combination of statins with gemfibrozil seems to increase risk of this adverse event, particularly in patients with renal impairment, more than combination with other lipid-lowering agents. Combination therapy with other agents including anticoagulants, antihypertensive, anti-inflammatory, oral hypoglycemic and antifungal agents as well as beta-blockers, H2 blockers, cyclosporine and digoxin has been also **reviewed**. The pleiotropic non-lipid lowering properties of statins and their effects on the quality of lipoprotein particles, the activities of cholesteryl ester transfer protein and lecithin:cholesterol acyltransferase as well as their possible synergistic effects with n-3 fatty acids, phytosterols, vitamin E and aspirin in reducing cardiovascular events warrant further investigation.

L11 ANSWER 4 OF 4 MEDLINE on STN
AN 97060197 MEDLINE
DN 97060197 PubMed ID: 8904518
TI Triglyceride-rich lipoproteins in non-insulin-dependent diabetes mellitus: post-prandial metabolism and relation to premature atherosclerosis.
AU De Man F H; Cabezas M C; Van Barlingen H H; Erkelens D W; de Bruin T W
CS Department of Internal Medicine, University Hospital, Utrecht University, The Netherlands.
SO EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (1996 Feb) 26 (2) 89-108.
Ref: 264
Journal code: 0245331. ISSN: 0014-2972.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970312
AB Non-insulin-dependent diabetes mellitus is frequently associated with premature atherosclerosis. Abnormalities in lipid and lipoprotein metabolism contribute to the increased risk of coronary heart disease. One of the most common lipid abnormalities in non-insulin-dependent diabetes mellitus is hypertriglyceridaemia. In the present paper, the authors **review** the metabolism of triglyceride-rich lipoproteins, with special emphasis on the post-prandial state. Several studies have demonstrated that levels of atherogenic post-prandial lipoproteins are increased in patients with non-insulin-dependent diabetes mellitus. An increased supply of glucose and free fatty acids contributes to overproduction of very low-density lipoproteins, increasing the burden of triglyceride-rich lipoproteins on the common lipolytic pathway at the level of lipoprotein lipase. Low lipoprotein lipase activity and increased amounts of lipolysis-inhibiting free fatty acids further impair lipolysis of post-prandial lipoproteins. The clearance of atherogenic remnants is also delayed in non-insulin-dependent diabetes mellitus. There is evidence that a relative hepatic removal defect exists, secondary to impaired remnant-receptor **interaction** and increased competition with very low density lipoprotein remnants. Correction of the increased post-prandial lipaemia in non-insulin-dependent diabetes mellitus is advisable, as it may contribute to attenuation of the risk on premature atherosclerosis. When dietary measures and hypoglycaemic agents have failed to achieve acceptable lipid levels, lipid-lowering **drugs** should be advised. Fibric acids and hydroxymethyl-glutaryl coenzyme A (**HMG CoA**) **reductase** inhibitors are the **drugs** of choice.

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ILE 'HOME' ENTERED AT 14:34:47 ON 04 DEC 2003

=> file medline
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.21 | 0.21

FILE 'MEDLINE' ENTERED AT 14:34:58 ON 04 DEC 2003

FILE LAST UPDATED: 2 DEC 2003 (20031202/UP). FILE COVERS 1958 TO DATE.

On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s hmg coa reductase
         7768 HMG
        25419 COA
        50066 REDUCTASE
L1       3803 HMG COA REDUCTASE
              (HMG(W)COA(W)REDUCTASE)

=> s l1 and inhibitor/
'INHIBITOR/' IS NOT A VALID FIELD CODE
For a list of field codes for the current file, enter "HELP SFIELDS"
at an arrow prompt (=>).

=> s l1 and inhibitor?
       674878 INHIBITOR?
L2       2725 L1 AND INHIBITOR?

=> s l2 and alzheimer's
MISMATCHED QUOTE 'ALZHEIMER'S'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l2 and alzheimer?
        40435 ALZHEIMER?
L3         17 L2 AND ALZHEIMER?

=> d bib abs

L3   ANSWER 1 OF 17     MEDLINE on STN
AN   2003497241     IN-PROCESS
DN   22936000   PubMed ID: 14574624
TI   Brain cholesterol, statins and Alzheimer's Disease.
AU   Kirsch C; Eckert G P; Koudinov A R; Muller W E
CS   Department of Pharmacology, Biocenter Niederursel, University of
     Frankfurt, Frankfurt/M, Germany.
SO   PHARMACOPSYCHIATRY, (2003 Sep) 36 Suppl 2 S113-9.
     Journal code: 8402938. ISSN: 0176-3679.
CY   Germany: Germany, Federal Republic of
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 20031024
     Last Updated on STN: 20031108
AB   Growing evidence suggests that cellular cholesterol homeostasis is
     causally involved in different steps leading to pathological events in the
     brain of Alzheimer's Disease (AD) patients. It was previously
     demonstrated that the processing of the amyloid beta-peptide precursor
     protein (APP) is modulated by pronounced alterations in cellular
     cholesterol levels using statins or cholesterol extracting agents.
     However, a cholesterol-rich diet was found to enhance amyloid beta-peptide
     (Abeta) burden in the brain of transgenic mice without clearly affecting
     total brain cholesterol levels. Recent retrospective epidemiological
     studies have reported that the use of statins potentially suppresses the
     development of AD. Although some HMG-CoA
     reductase inhibitors seem to influence the central
     cholesterol pool in vivo, the above epidemiological findings are probably
     not linked to statin-induced changes in brain membrane cholesterol levels
     per se since not all statins active in preventing AD enter the central
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nervous system (CNS). Recently, we reported that different statins, regardless of their brain availability, induce alterations in cellular cholesterol distribution in the brain. Such pleiotropic, cholesterol-synthesis independent statin effects might be indirect and are possibly mediated at the blood-brain barrier (BBB) via nitric oxide (NO) or apolipoprotein E (ApoE).

=> d 10-17 bib abs

L3 ANSWER 10 OF 17 MEDLINE on STN
AN 2002181004 MEDLINE
DN 21898302 PubMed ID: 11900994
TI Pharmacological concentrations of the **HMG-CoA reductase inhibitor** lovastatin decrease the formation of the **Alzheimer** beta-amyloid peptide in vitro and in patients.
AU Buxbaum Joseph D; Cullen Edward I; Friedhoff Lawrence T
CS Laboratory of Molecular Neuropsychiatry, Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA.. buxbaj01@doc.mssm.edu
NC AG02219 (NIA)
AG10491 (NIA)
SO FRONTIERS IN BIOSCIENCE, (2002 Apr 1) 7 a50-9.
Journal code: 9702166. ISSN: 1093-4715.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 20020401
Last Updated on STN: 20020416
Entered Medline: 20020415
AB Epidemiological studies demonstrate that hypercholesterolemia is a risk factor for **Alzheimer**'s disease (AD). As the generation and accumulation of the beta-amyloid peptide (Abeta) in the brain appears to be significant for the initiation and progression of AD, it is possible that cholesterol levels regulate Abeta formation and/or clearance. To test the effects of altering cholesterol on Abeta formation, we incubated cells with or without lovastatin acid, the active metabolite of the **HMG-CoA reductase inhibitor** lovastatin, and measured the fraction of Abeta formed from its precursor under each condition. We observed that treatment with lovastatin acid led to a profound decrease in the levels of Abeta formed. This effect was observed at concentrations of 0.05-5 microM, ranges where this compound is effective at inhibiting **HMG-CoA reductase**.
To examine the effects of lovastatin on Abeta in vivo, human subjects who had elevated low-density lipoprotein cholesterol were treated during a double-blind, randomized study with 10-60-mg once-daily doses of a controlled-release formulation of lovastatin, or matching placebo. Serum Abeta concentrations were measured before and after up to 3 months of treatment. Mean and median changes from baseline in serum Abeta concentrations showed a significant ($p < 0.0348$), dose-dependent decrease. Differences between the 40- and 60-mg dose groups and placebo were statistically significant (Dunnett's $p< 0.05$). Our results suggest a mechanism by which hypercholesterolemia may increase risk for AD and indicate that lovastatin reduces Abeta formation and may thereby be effective in delaying the onset and/or slowing the progression of AD.

L3 ANSWER 11 OF 17 MEDLINE on STN
AN 2002156960 MEDLINE
DN 21885785 PubMed ID: 11888511
TI Statins inhibit A beta-neurotoxicity in vitro and A beta-induced vasoconstriction and inflammation in rat aortae.
AU Paris Daniel; Townsend Kirk P; Humphrey James; Obregon Demian F; Yokota Kiyoko; Mullan Michael
CS Department of Psychiatry, The Roskamp Institute, University of South Florida, 3515 E. Fletcher Avenue, Tampa, FL 33613, USA.. dparis@hsc.usf.edu
SO ATHEROSCLEROSIS, (2002 Apr) 161 (2) 293-9.
Journal code: 0242543. ISSN: 0021-9150.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020313

Last Updated on STN: 20020515
Entered Medline: 20020514

AB Freshly solubilized A beta peptides synergistically increase the magnitude of the constriction induced by endothelin-1 (ET-1), via the activation of a pro-inflammatory pathway. We report that mevinolin and mevastatin, two **inhibitors** of the 3-hydroxy-3-methylglutaryl coenzyme A (**HMG-CoA**) **reductase** are able to completely abolish the vasoactive properties of A beta in rat aortae. Mevinolin also appears to oppose the increased vascular reactivity to ET-1 induced by interleukin 1-beta and phospholipase A(2) suggesting that statins display some anti-inflammatory properties. We show that freshly solubilized A beta stimulates prostaglandin E(2) and F(2 alpha) production (by 6 and 3.6 times, respectively) in isolated rat aortae and that mevinolin completely antagonizes this effect confirming the anti-inflammatory action of mevinolin ex vivo in rat aortae. In addition, we observed that A beta vasoactivity is not mediated nor modulated by mevalonic acid suggesting that the anti-inflammatory action of the statins are not related to an inhibition of **HMG-CoA reductase** activity.
Differentiated human neuroblastoma cells (IMR32) were used to assess the neurotoxic effect of pre-aggregated A beta by quantifying the release of lactate dehydrogenase (LDH) in the cell culture medium. A beta appears to enhance LDH release by 30% in IMR32 cells, an effect that can be completely opposed by mevastatin. Taken together these data show that statins can antagonize the effect of A beta in different assays and provide new clues to understand the prophylactic action of the statins against **Alzheimer**'s disease.

L3 ANSWER 12 OF 17 MEDLINE on STN
AN 2001540089 MEDLINE
DN 21472482 PubMed ID: 11588606
TI 3-hydroxy-3-methylglutaryl-coenzyme A reductase mRNA in **Alzheimer** and control brain.
AU Yasojima K; McGeer E G; McGeer P L
CS Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, V6T 1Z3, Canada.
SO NEUROREPORT, (2001 Sep 17) 12 (13) 2935-8.
Journal code: 9100935. ISSN: 0959-4965.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Statins are widely used pharmaceutical agents which lower plasma cholesterol by inhibiting the rate controlling enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (**HMG-CoA**) **reductase**.
One epidemiological study suggests that statin therapy may provide protection against **Alzheimer** disease (AD). The aim of the present study was to determine the relative expression of **HMG-CoA reductase** mRNAs in various areas of brain as well as in peripheral organs and to compare values in AD and control cases. High levels of the mRNA were found in all areas of brain but no obvious differences were found between AD and controls. We conclude that brain has a robust capacity to synthesize cholesterol which appears to be unaffected by AD pathology.

L3 ANSWER 13 OF 17 MEDLINE on STN
AN 2001524323 MEDLINE
DN 21455625 PubMed ID: 11571339
TI Cholesterol and **Alzheimer**'s disease: is there a link?.
CM Comment in: Neurology. 2002 Apr 9;58(7):1135
Comment in: Neurology. 2002 Jul 9;59(1):150; author reply 150-1
AU Simons M; Keller P; Dichgans J; Schulz J B
CS Department of Neurology, University of Tubingen, Germany..
mika_simons@hotmail.com
SO NEUROLOGY, (2001 Sep 25) 57 (6) 1089-93.
Journal code: 0401060. ISSN: 0028-3878.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200110
ED Entered STN: 20010926
Last Updated on STN: 20030117
Entered Medline: 20011018

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AB The Abeta-amyloid peptide (Abeta), the main component of amyloid plaques, is derived by proteolytic cleavage from the amyloid precursor protein (APP). Epidemiologic and biochemical data suggest a link between cholesterol, APP processing, Abeta, and **Alzheimer**'s disease. Two recent epidemiologic studies indicate that there is a decreased prevalence of AD associated with the use of cholesterol-lowering drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (**HMG -CoA reductase inhibitors** or statins). Experiments in cell culture and in vivo demonstrate that treatment with statins reduces production of Abeta. The authors discuss how cholesterol might modulate Abeta deposit formation. As neurons receive only small amounts of exogenous cholesterol, statins that efficiently cross the blood-brain barrier may reduce the amount of neuronal cholesterol below a critical level. Decreased neuronal cholesterol levels inhibit the Abeta-forming amyloidogenic pathway possibly by removing APP from cholesterol- and sphingolipid-enriched membrane microdomains. In addition, depletion of cellular cholesterol levels reduces the ability of Abeta to act as a seed for further fibril formation. These intriguing relationships raise the hopes that cholesterol-lowering strategies may influence the progression of AD.

L3 ANSWER 14 OF 17 MEDLINE on STN
AN 2001447976 MEDLINE
DN 21198717 PubMed ID: 11303752
TI Differential effects of lovastatin treatment on brain cholesterol levels in normal and apoE-deficient mice.
AU Eckert G P; Kirsch C; Mueller W E
CS Department of Pharmacology, Biocenter Niederursel, University of Frankfurt, Germany.
SO NEUROREPORT, (2001 Apr 17) 12 (5) 883-7.
Journal code: 9100935. ISSN: 0959-4965.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB Growing evidence indicates that membrane cholesterol is involved in the development of **Alzheimer**'s disease. Therefore, the availability of pharmacological strategies to modify brain cholesterol is of increasing importance. Accordingly, we investigated the effects of the **HMG -CoA reductase inhibitor** lovastatin on brain cholesterol levels in vivo. Brain cholesterol was significantly decreased by lovastatin treatment (100 mg/kg/day) in 1- and 12-month-old C57BL/6J mice. Reduced brain cholesterol was associated with decreased pyrene-excimer fluorescence, indicating altered membrane function. Lovastatin had no effect on brain cholesterol ApoE-/- mice. Peripheral cholesterol levels were not affected by lovastatin in all three groups of mice. We demonstrate for the first time that lovastatin represents a valid pharmacological tool to significantly modulate brain cholesterol levels.

L3 ANSWER 15 OF 17 MEDLINE on STN
AN 2001441857 MEDLINE
DN 21380454 PubMed ID: 11487306
TI Essential fatty acids as possible mediators of the actions of statins.
AU Das U N
CS EFA Sciences LLC, 1420 Providence Highway, Norwood, MA 02062, USA.. undurti@hotmail.com
SO PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, (2001 Jul) 65 (1) 37-40. Ref: 48
Journal code: 8802730. ISSN: 0952-3278.
CY Scotland: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010813
Last Updated on STN: 20011008
Entered Medline: 20011004
AB Statins and polyunsaturated fatty acids have similar actions: both enhance endothelial nitric oxide synthesis, inhibit the production of pro-inflammatory cytokines, lower cholesterol levels, prevent atherosclerosis and are of benefit in coronary heart disease, stroke and

osteoporosis. Statins enhance the conversion of linoleic acid and eicosapentaenoic acid to their long chain derivatives. Animals with essential fatty acid deficiency show an increase in **HMG-CoA reductase** activity, which reverts to normalcy following topical application of linoleic acid. Similarly to statins, polyunsaturated fatty acids also inhibit **HMG-CoA reductase** activity. In view of the similarity in their actions and as statins influence essential fatty acid metabolism, it is suggested that essential fatty acids and their metabolites may serve as second messengers of the actions of statins.

L3 ANSWER 16 OF 17 MEDLINE on STN
AN 2001386992 MEDLINE
DN 21334450 PubMed ID: 11440749
TI Use of statins in CNS disorders.
AU Cucchiara B; Kasner S E
CS Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA.
SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (2001 Jun 15) 187 (1-2) 81-9. Ref: 112
Journal code: 0375403. ISSN: 0022-510X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200109
ED Entered STN: 20010910
Last Updated on STN: 20010910
Entered Medline: 20010906
AB It is well established that 3-hydroxy-3-methyglutaryl coenzyme A (**HMG-CoA**) **reductase inhibitors** ("statins") reduce cholesterol levels and prevent coronary heart disease (CHD). Although a causal relation between elevated cholesterol levels and stroke has not been well defined, a number of large secondary prevention studies and meta-analyses have shown that statin therapy reduces stroke in patients with CHD and hypercholesterolemia. In addition to the vascular effects of statins (stabilization of atherosclerotic plaques, decreased carotid intimal-medial thickness), there are increasing data to suggest that these agents have additional properties that are potentially neuroprotective. These include endothelial protection via actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory and anti-platelet effects. These actions of statins might have potential uses in other neurological disorders such as **Alzheimer**'s disease and certain types of brain tumors.

L3 ANSWER 17 OF 17 MEDLINE on STN
AN 1999429668 MEDLINE
DN 99429668 PubMed ID: 10501560
TI The role of cholesterol in the biosynthesis of beta-amyloid.
AU Frears E R; Stephens D J; Walters C E; Davies H; Austen B M
CS Neurodegeneration Unit, St George's Hospital Medical School, London, UK.
SO NEUROREPORT, (1999 Jun 3) 10 (8) 1699-705.
Journal code: 9100935. ISSN: 0959-4965.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991115
AB Addition of the beta-hydroxy-beta-methylglutaryl-CoA (**HmG-CoA**) **reductase inhibitor** lovastatin to human HEK cells transfected with the amyloid precursor protein (APP) reduces intracellular cholesterol/protein ratios by 50%, and markedly inhibits beta-secretase cleavage of newly-synthesized APP. Exogenous water-solubilized cholesterol at 200 microg/ml concentration increases newly synthesized beta-amyloidogenic products four-fold. These intracellular changes are detectable by immunoprecipitation and immunofluorescent labelling. Analyses of the fragments captured from culture medium by an N-terminal anti-beta-amyloid antibody on ProteinChip arrays and detected using surface-enhanced laser desorption/ionization (SELDI) mass spectrometry revealed that culture with cholesterol (200 microg/ml) increased secretion of beta-amyloid 1-40 by 1.8-fold, and increased secretion of beta-amyloid 1-42. Changes in APP processing by

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cholesterol may mediate the way in which the ApoE4 allele increases risk of developing **Alzheimer**'s disease (AD) in western populations.

=> d 2-9 bib abs

L3 ANSWER 2 OF 17 MEDLINE on STN
AN 2003436571 MEDLINE
DN 22856852 PubMed ID: 13677244
TI [Pleiotrophic effect of statins (3-hydroxy-3-methylglutaryl-coenzyme a reductase **inhibitors**)].
Pleiotrophe Effekte von Statinen (3-Hydroxy-3-Methylglutaryl-Coenzym A-Reduktasehemmer).
AU Igel Michael; Sudhop Thomas; von Bergmann Klaus
CS Abteilung fur Klinische Pharmakologie, Universitatsklinikum Bonn.. michael.igel@uni-bonn.de
SO ARZNEIMITTEL-FORSCHUNG, (2003) 53 (8) 545-53. Ref: 98
Journal code: 0372660. ISSN: 0004-4172.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
FS Priority Journals
EM 200310
ED Entered STN: 20030919
Last Updated on STN: 20031008
Entered Medline: 20031006
AB The development of statins improved the therapy of hypercholesterolemia and atherosclerotic disease tremendously. The beneficial effects of statins were clearly demonstrated in large scale primary and secondary prevention studies. In addition to the reduction of plasma cholesterol, inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (**HMG-CoA**) **reductase** also results in the depletion of intermediates of cholesterol biosynthesis that are important for cellular integrity. The so called pleiotrophic effects of statins and probably also their adverse events can be attributed to the inhibition of synthesis of these intermediates. The review article describes the pathogenesis of atherosclerosis, the pharmacokinetic and pharmacodynamik of statins, and their pleiotrophic effects concerning endothelial function, LDL (low density lipoprotein) oxidation, macrophages, smooth muscle cell proliferation, atherosclerotic plaque, platelets, thrombosis, proinflammatory factors, haemorheology, hypertension, venous thrombosis, bone metabolism, stroke, and the possible influence on the prevention of **Alzheimer**'s disease.

L3 ANSWER 3 OF 17 MEDLINE on STN
AN 2003100900 MEDLINE
DN 22500578 PubMed ID: 12613664
TI Cerivastatin: a cellular and molecular drug for the future?.
AU Siegel-Axel D I
CS Department of Medicine III (Cardiology), University of Tubingen, Otfried-Muller St. 10, D-72076 Tubingen, Germany.. daaxel@med.uni-tuebingen.de
SO CELLULAR AND MOLECULAR LIFE SCIENCES, (2003 Jan) 60 (1) 144-64. Ref: 166
Journal code: 9705402. ISSN: 1420-682X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030305
Last Updated on STN: 20030331
Entered Medline: 20030328
AB The 'statin story' began in 1987 when the first-generation, fungal **HMG-CoA reductase inhibitor** lovastatin received FDA approval in the USA. Ten years later, the sixth compound of this class came onto the world market--the fully synthetic statin cerivastatin. A number of clinical studies had confirmed its high pharmacological efficacy, its excellent pharmacokinetic properties with fast and nearly complete absorption after oral uptake, a linear kinetic over a broad concentration range, and its favorable safety profile. The greatest advantages, of cerivastatin, however, are its lipophilicity, its high bioavailability of about 60% after oral application and its potency at 100-fold lower doses compared to other lipophilic statins. Nevertheless, the most exciting findings are certainly its

non-lipid-related, pleiotropic effects at the cellular and molecular level. Statin therapy was also found to reduce mortality in cases where cholesterol levels or atherosclerotic plaque formation remained unaltered. However, cerivastatin improves endothelial dysfunction, possesses anti-inflammatory, antioxidant, anticoagulant, antithrombotic, antiproliferative, plaque-stabilizing, immunmodulatory, and angiogenic effects, and may even prevent tumor growth, **Alzheimer**'s disease, and osteoporosis. Most of these effects seem to be based on the inhibition of isoprenoid synthesis. Although cerivastatin is no longer on the market because of some problematic side effects, it could be one of the most potent cellular and molecular drugs for the future.

L3 ANSWER 4 OF 17 MEDLINE on STN
AN 2003071400 MEDLINE
DN 22469350 PubMed ID: 12582450
TI Therapeutic approaches to the treatment of **Alzheimer**'s disease.
AU Yamada Kiyofumi; Toshitaka Nabeshima
CS Laboratory of Experimental Therapeutics, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa, Japan.
SO Drugs Today (Barc), (2002 Sep) 38 (9) 631-7. Ref: 47
Journal code: 101160518. ISSN: 0025-7656.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030214
Last Updated on STN: 20030305
Entered Medline: 20030304
AB **Alzheimer**'s disease is the most common cause of progressive decline of cognitive function in aged humans and is characterized by the presence of numerous senile plaques and neurofibrillary tangles accompanied by neuronal loss. The only treatment currently available for the disease is pharmacotherapy with acetylcholinesterase **inhibitors**, a palliative strategy aimed at the temporary improvement of cognitive function. Other strategies with disease-modifying potential may include the use of antiinflammatory drugs, estrogen replacement therapy and antioxidants. Recent progress in understanding the molecular and cellular pathophysiology of **Alzheimer**'s disease has suggested possible pharmacological interventions that could modify the development and progress of the disease (disease-modifying therapy), such as treatment with secretase **inhibitors**, transition metal chelators, **HMG-CoA reductase inhibitors** and amyloid-b immunization. **Inhibitors** of tau hyperphosphorylation may also modulate the development and progress of the disease.

L3 ANSWER 5 OF 17 MEDLINE on STN
AN 2003028385 MEDLINE
DN 22423174 PubMed ID: 12534972
TI Blockade of **HMG-CoA reductase** activity causes changes in microtubule-stabilizing protein tau via suppression of geranylgeranylpyrophosphate formation: implications for **Alzheimer**'s disease.
AU Meske V; Albert F; Richter D; Schwarze J; Ohm T G
CS Institute of Anatomy, Charite, Philippstrasse 12, D-10115 Berlin, Germany.. V.Meske@gmx.de
SO EUROPEAN JOURNAL OF NEUROSCIENCE, (2003 Jan) 17 (1) 93-102.
Journal code: 8918110. ISSN: 0953-816X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030122
Last Updated on STN: 20030429
Entered Medline: 20030428
AB Histopathologically, **Alzheimer**'s disease is characterized by plaques and tangles that develop progressively over time. Experimental data described a statin-induced decrease in beta-amyloid production, a major constituent of the plaques. Others reported data on statin-mediated changes in neuronal survival and cytoskeleton, including the microtubule-associated protein tau, a major constituent of the tangles. However, these latter reports remain contradictory. To clarify and extend our knowledge on the effect of statin on the cytoskeleton, we challenged

rat primary neuron cultures by lovastatin and determined the metabolite that is critical for structural integrity and survival of neurons. During the blockade of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the neuritic network was affected and eventually was completely destroyed. This process was not part of the execution phase of apoptosis and was marked by alterations in the microfilament and microtubule system. The distribution and phosphorylation of protein tau changed. Immunoblot analysis and indirect immunofluorescence revealed a transient increase in tau phosphorylation, which ceased during the execution of apoptosis. All of these effects could be linked to the lack of the geranylgeranylpyrophosphate intermediate. Inhibition of the geranylgeranylation of Rho family GTPases (geranylgeranyl-transferase I) evoked similar changes in neurons. These data and our findings that statin treatment reduced the membrane-bound fraction of RhoA-GTPase in neurons suggest that reduced levels of functional small G proteins are responsible for the observed effects. Our data demonstrate that lovastatin concentrations able to suppress not only cholesterol but also geranylgeranylpyrophosphate formation may evoke phosphorylation of tau reminiscent of preclinical early stages of **Alzheimer**'s disease and, when prolonged, apoptosis.

L3 ANSWER 6 OF 17 MEDLINE on STN
AN 2003009523 MEDLINE
DN 22403801 PubMed ID: 12515562
TI The pleiotropic effects of **HMG-CoA reductase inhibitors**: their role in osteoporosis and dementia.
AU Waldman Alla; Kritharides Leonard
CS Department of Cardiology, Concord Hospital, University of Sydney, NSW, Australia.
SO DRUGS, (2003) 63 (2) 139-52. Ref: 104
Journal code: 7600076. ISSN: 0012-6667.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030108
Last Updated on STN: 20030416
Entered Medline: 20030414
AB **HMG-CoA reductase** is the rate-limiting enzyme for cholesterol synthesis and its inhibition exerts profound effects on cellular metabolism. **Inhibitors** of this enzyme are used in clinical practice to lower plasma cholesterol levels and are commonly collectively referred to as 'statins'. A number of in vitro, in vivo animal, and clinical studies suggest that properties of statins other than cholesterol lowering may be of biological importance. These diverse properties are often referred to as 'pleiotropic' and suggest that statins may affect a number of diseases of ageing. In this article we review the biological plausibility and clinical evidence of a role for statins in modulating two diseases of ageing: osteoporosis and dementia (including **Alzheimer**'s disease). In both diseases, there is a sound cellular and laboratory basis for a plausible therapeutic effect of statins. In the case of osteoporosis, there are conflicting data regarding clinical benefit, with both negative and positive results reported. In particular, secondary analyses of randomised, controlled studies have shown no reduction of fracture risk by statins. In the case of dementia there are fewer clinical studies but there is clear anticipated benefit in macrovascular dementias attributable to statin-mediated reduction of the risk of stroke. Overall, there are a lack of prospective, placebo-controlled, randomised data testing statins and modulation of the risk of osteoporosis-related fracture or of clinical dementia, where these are primary outcomes. Until such data are available, the use of statins appears promising but cannot be recommended as a primary therapeutic modality for either condition.

L3 ANSWER 7 OF 17 MEDLINE on STN
AN 2002711560 IN-PROCESS
DN 22361747 PubMed ID: 12474023
TI **HMG-CoA reductase inhibitors** (statins) in the treatment of **Alzheimer**'s disease and why it would be ill-advise to use one that crosses the blood-brain barrier.
AU Sparks D L; Connor D J; Browne P J; Lopez J E; Sabbagh M N
CS D. Larry Sparks, Sun Health Research Institute, 10515 W. Santa Fe Drive, Sun City, Az 85351, USA. E-mail:. Larry.Sparks@SunHealth.org
SO JOURNAL OF NUTRITION, HEALTH & AGING, (2002) 6 (5) 324-31.
Journal code: 100893366. ISSN: 1279-7707.

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CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20021217
Last Updated on STN: 20021217
AB Increased circulating cholesterol has been long linked to an increased risk of coronary artery disease (CAD), and is now linked to an increased risk of developing **Alzheimer** s disease (AD). We first showed the neuropathologic link between CAD and AD as increased incidence of cerebral senile plaques in both disorders. We then showed that AD-like neuropathology occurred in the brains of cholesterol-fed rabbits; including increased -amyloid (Ab). Currently there are a number of transgenic mouse models of AD that exhibit enhanced Ab pathology if cholesterol diet is administered. Culture studies clearly show that excess cholesterol enhances beta-metabolism of amyloid precursor protein (APP) and production of -amyloidogenic peptides, and that sufficiently reducing cholesterol levels by inhibition of synthesis completely inhibits all beta-metabolism of APP. Our finding that the elevated levels of Ab in rabbits fed cholesterol diet could be cleared from the brain by resuming a control diet prompted the hypothesis that lowering cholesterol levels in the blood of AD patients may be of some clinical benefit. Pilot data suggests that therapeutically lowering circulating cholesterol may attenuate Ab production in the cholesterol-fed rabbit brain, may stabilize cognitive performance in mildly impaired AD patients, and may reduce the risk of developing AD. Accordingly, we have initiated a double-blind treatment trial evaluating Atorvastatin Na+ among 120 mild-to-moderately impaired AD subjects randomized to one of two groups receiving placebo or active drug once a day. Atorvastatin is one of a general class of **HMG-CoA reductase inhibitor** drugs called statins that lower cholesterol by inhibition of synthesis. We chose to use Atorvastatin in this AD Treatment Trial because it does not cross the blood-brain-barrier, and believe it would be ill-advised to use a statin that does. This position stems from the observations that excess cholesterol inhibits cholesterol synthesis and increases Ab production, that Ab kills cells in part by inhibiting cholesterol synthesis, and that statins acting at the neuronal level could further exacerbate degeneration in AD by further inhibition of necessary cholesterol synthesis.

L3 ANSWER 8 OF 17 MEDLINE on STN
AN 2002632540 MEDLINE
DN 22278366 PubMed ID: 12390056
TI Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults.
AU Carlsson Cynthia M; Papcke-Benson Kristi; Carnes Molly; McBride Patrick E; Stein James H
CS University of Wisconsin Medical School, Madison, Wisconsin 53792, USA.
SO DRUGS AND AGING, (2002) 19 (10) 793-805.
Journal code: 9102074. ISSN: 1170-229X.
CY New Zealand
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20021023
Last Updated on STN: 20030521
Entered Medline: 20030520
AB INTRODUCTION: Concerns about the effects of **HMG-CoA reductase inhibitors** ('statins') on health-related quality of life may contribute to their underuse in older adults with and at risk for cardiovascular disease. These concerns also may prevent clinicians from enrolling older patients in clinical trials assessing the efficacy of statins as a preventive therapy for **Alzheimer**'s disease. OBJECTIVE: To determine the effects of pravastatin and tocopherol (vitamin E), alone and in combination, on health-related quality of life in older adults. STUDY DESIGN: Double-blind, randomised, placebo-controlled, crossover study. PARTICIPANTS: Forty-one community-dwelling men and women aged > or = 70 years with low-density lipoprotein-cholesterol (LDL-C) > or = 3.62 mmol/L (140 mg/dl) participated. METHODS: Subjects received pravastatin for 6 months then pravastatin plus tocopherol for an additional 6 months (group 1), or tocopherol for 6 months then pravastatin plus tocopherol for an additional 6 months (group 2). Dosages were pravastatin 20 mg daily and tocopherol 400 IU daily. MAIN OUTCOME MEASURES: The following health-related quality-of-life measures were assessed at baseline, after 6 months and after 1 year: health perception, depression, physical function, cognitive

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function and sleep behaviour. In addition, data on adverse effects and laboratory abnormalities were obtained. RESULTS: Pravastatin reduced levels of total cholesterol (-21%, p < 0.001) and LDL-C (-29%, p < 0.001). Health-related quality-of-life scores, physical adverse effects, muscle enzyme levels and liver function tests did not change after 12 months of therapy with pravastatin, tocopherol or their combination. CONCLUSION: Both pravastatin and tocopherol have a good safety profile, are well tolerated and do not adversely affect health-related quality of life in older patients with hypercholesterolaemia. Given the significant beneficial cardiovascular effects of statin therapy in older adults and the potential role of statins in prevention of **Alzheimer**'s disease, concerns about adverse effects on quality of life should not deter use of these medications in this population.

L3 ANSWER 9 OF 17 MEDLINE on STN
AN 2002438630 MEDLINE
DN 22183872 PubMed ID: 12196129
TI Cholesterol and **Alzheimer**'s disease.
AU Wolozin B
CS Department of Pharmacology, Loyola University Medical Center, Bldg. 102, Rm. 3634, 2160 South First Avenue, Maywood, IL 60153, USA..
bwolozi@lumc.edu
NC AG/NS17485-01A2 (NIA)
SO BIOCHEMICAL SOCIETY TRANSACTIONS, (2002 Aug) 30 (4) 525-9. Ref: 28
Journal code: 7506897. ISSN: 0300-5127.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020829
Last Updated on STN: 20030225
Entered Medline: 20030224
AB Accumulation of a 40-42-amino acid peptide, termed amyloid-beta peptide (A beta), is associated with **Alzheimer**'s disease (AD), and identifying medicines that inhibit A beta could help patients with AD. Recent evidence suggests that a class of medicines that lower cholesterol by blocking the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (**HMG-CoA reductase**), termed statins, can inhibit A beta production. Increasing evidence suggests that the enzymes that generate A beta function best in a high-cholesterol environment, which might explain why reducing cholesterol would inhibit A beta production. Studies using both neurons and peripheral cells show that reducing cellular cholesterol levels, by stripping off the cholesterol with methyl-beta-cyclodextrin or by treating the cells with **HMG-CoA reductase inhibitors**, decreases A beta production. Studies performed on animal models and on humans concur with these results. In humans, lovastatin, an **HMG-CoA reductase inhibitor**, has been shown to reduce A beta levels in blood of patients by up to 40%. The putative role of A beta in AD raises the possibility that treating patients with statins might lower A beta, and thereby either delay the occurrence of AD or retard the progression of AD. Two large retrospective studies support this hypothesis. Both studies suggest that patients taking statins had an approx. 70% lower risk of developing AD. Since statins are widely used by doctors, their ability to reduce A beta offers a putative therapeutic strategy for treating AD by using medicines that have already been proved safe to use in humans.